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The Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville MD, 20852
http://www.fda.gov/dockets/ecomments

RE: Docket No 2003N-0502 – Agency Information Collection Activities; Proposed Collection; Comment Request; Study to Measure the Compliance of the Use of Triptans in Migraine Headache Patients With Vascular Disease. Federal Register/Vol. 68, No. 221/November 17, 2003

Agency: Food and Drug Administration

Dear Sir/Madam:

On behalf of the American Headache Society, we are writing in response to the Agency's request for comments on a proposed internet-based questionnaire to measure the compliance of prescribers with the contraindication of the use of triptans in migraine headache patients with vascular disease. Each questionnaire will require an estimated 2 hours to complete. This study will use the Internet to recruit 500 triptan-using migraine headache patients to measure the proportion of patients that were prescribed triptans despite having pre-existing cardiovascular, cerebrovascular, or peripheral vascular syndromes. A sample of patients' medical records will then be solicited and reviewed to verify the medical history and estimate the prevalence of vascular ischemic syndromes among patients using triptans.

Migraine, which affects approximately 1 in 10 individuals, is pervasive and often debilitating. Migraine restricts or prevents normal activities, and patients are often bedridden until symptoms subside. In the 1999 US population-based American Migraine

Study II, 91% of migraineurs indicated that their severe headaches cause at least some disability; and more than half (53%) reported substantial impairment in activity or the requirement for bed rest with their severe headaches.[1]

According to the US Headache Consortium Guidelines, triptans are recommended for migraine sufferers with moderate to severe pain and constitute the mainstay of migraine-specific prescription therapy in the United States.[2] Unfortunately, fewer than half of migraine sufferers in the United States receive any prescription medicine for their headaches, less than one-third of patients are very satisfied with their acute therapy, and fewer than 20% of have ever received a triptan.[1,3,4]

Although the relatively restricted use of triptans may be attributed to several factors, research suggests that prescribers' concerns about cardiovascular safety prominently figure in limiting their use.[5] These concerns are derived from isolated reports of serious cardiovascular adverse events in patients exposed to a triptan and the occurrence of chest symptoms as a well recognized side effect.

In view of these concerns, the disability and cost associated with migraine, and the under-utilization of triptans in appropriate patients, the American Headache Society convened the ***Triptan Cardiovascular Safety Expert Panel*** to evaluate the scientific and clinical data on triptan-associated cardiovascular risk and to formulate consensus recommendations to guide health care providers in making informed prescribing decisions for patients with migraine. The Triptan Cardiovascular Safety Expert Panel (the Panel) was composed of a multidisciplinary group of experts in neurology, primary care, cardiology, pharmacology, women's health, and epidemiology.

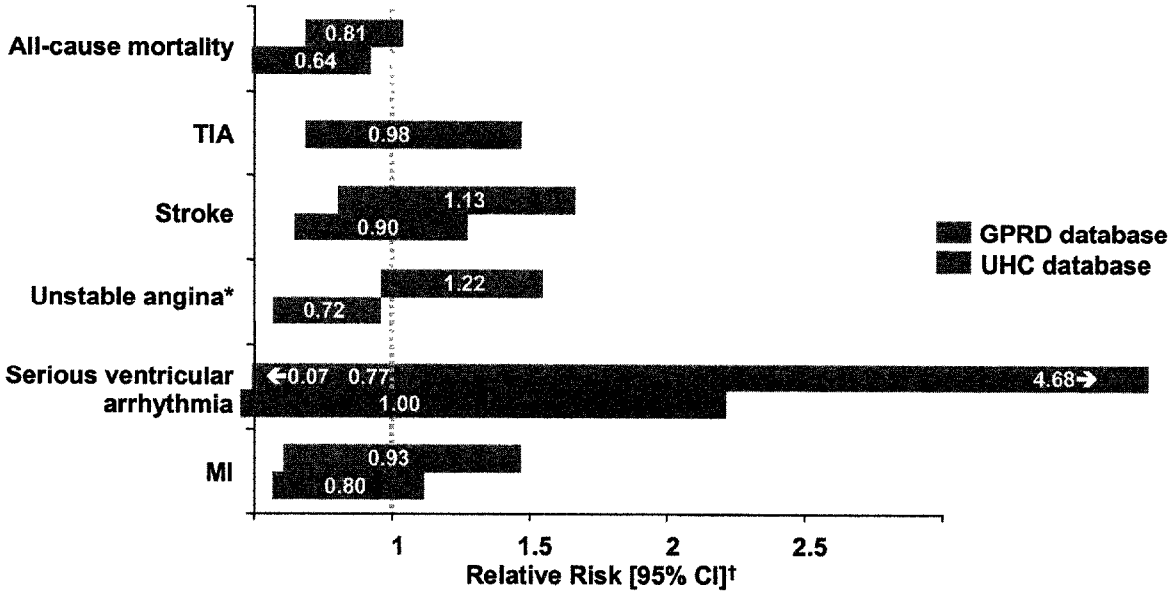
From this exhaustive and extensive review of the results from clinical trials, postmarketing surveillance and pharmacodynamic studies, the Panel concluded that triptans are generally safe and well-tolerated.[6] The incidence of triptan-associated serious cardiovascular adverse events in both clinical trials and clinical practice appears to be extremely low (less than 1 per 1 million persons treated).[6,7] Chest symptoms occurring during use of triptans in clinical trials are not related to myocardial ischemia, and several lines of evidence suggest that non-ischemic mechanisms are responsible for

triptan-associated chest symptoms, although the mechanism of chest symptoms has not been clearly defined to date.

The panel also concluded that in patients at low risk of coronary artery disease, triptans can be prescribed confidently without the need for prior cardiovascular evaluation. However, because the vast majority of clinical-trials and clinical-practice data on triptans are derived from patients without known coronary artery disease, this recommendation cannot be extrapolated to patients with established cardiovascular disease or for those at high risk for silent or unrecognized myocardial ischemia. The panel recommends that physicians view the low probability of the cardiovascular risk of triptans in the context of the benefits of treatment for individual patients with migraine.

Contrary to the comment made in the Federal Register, there are estimates available concerning the rates of various vascular diseases and cardiac risk factors among patients using triptans. Recently, the association between the use of triptans in migraine sufferers and the incidence of cardiovascular and cerebrovascular events was reported from an analysis of two large managed-care prescription database studies.[8,9] Using the United Healthcare database in the United States and the General Practice Research Database (GPRD) in the United Kingdom, the authors were able to identify all patients receiving triptans using pharmacy data and then determine rates of vascular disease and risk factors both before and after prescribing. In this way, information and recall bias was avoided by linking medical claims and pharmacy databases. These studies demonstrated a relative risk ratio of less than 1 for serious cardiovascular and cerebrovascular events, as well as all-cause mortality, for migraine patients treated with triptans compared with those not receiving triptan therapy (figure 1).

Adjusted Relative Risk [95% CI] of Vascular Event and Death by Use of Triptan Among Migraineurs [8,9]



One strength of the above referenced studies is that they capture a systematic sample of everyone treated with a triptan within a particular health system. In contrast, the proposed Internet-based questionnaire study has a number of methodological limitations (outlined below) that may produce misleading data and lead to a renewed and unnecessary sense of alarm amongst patients and practitioners. As a consequence, under-treatment may be perpetuated or even accentuated based on a misunderstanding of risks and benefits.

Information derived from this survey will have limited validity for a number of reasons. First, selection bias is a major concern in all Internet surveys and particularly for this study. The respondents to this survey are self-selected, have little incentive to complete an internet questionnaire, and are therefore more likely to have suffered adverse events from the use of triptans. Moreover, in the absence of a true denominator, the prevalence of vascular disorders which contraindicate the use of triptans is not possible to calculate with accuracy. Because migraine is a disorder more common in individuals with low education and low SES, and internet users have higher SES on average, the study may select against a large group of migraine sufferers. This design will permit a demonstration that some migraine sufferers receive triptans despite cardiovascular

relative contra-indications; it will not allow us to estimate the prevalence or incidence of inappropriate prescribing.

The lack of accuracy of patient self-reporting of medical diagnoses and the timing of adverse events could also lead to significant information and recall bias. In addition, the significance of a reported adverse vascular outcome in a respondent who has used a triptan in the past may be unclear. From the Cardiovascular Safety Expert Panel review of post-marketing surveillance reports of adverse vascular outcomes in patients using triptans, it is clear that the temporal relationship between the administration of a triptan and the reported outcome would not be consistent with a causal relationship in many cases. Unfortunately, the medical records of only a subset of patients in this study will be solicited to corroborate the medical history reported by respondents. With a lack of veracity in assuring the accuracy of the medical information reported, it will be difficult and inadvisable to draw meaningful conclusions from this method of case ascertainment.

Furthermore, the dynamic environment, process of informed consent, and clinical decision-making which takes place in the context of a private patient-physician encounter, cannot be reliably reproduced even with accurate completion of the questionnaire and ascertainment of the medical record.

Finally, the completion of a web-based questionnaire, and thus the provision of an Internet address, might violate the Health Insurance Portability and Accountability Act (HIPPA) regulations regarding medical privacy, which were enacted in April 2003.

The study protocol must be explicit and address:

1. A strategy for identifying a representative sample of migraine sufferers treated with triptans.
2. The method by which this population is contacted and the description of the rationale and purpose of the study used to convince patients to complete the lengthy questionnaire. The method must be free of bias and coercion.
3. The rationale and power calculations used to define the required number of 500 participants.
4. The relevant and complete medical records of all respondents must be reviewed. In addition, the method by which additional medical information will be acquired

for cases which are incomplete must be addressed, or the criteria for discarding a case when the necessary medical data is incomplete must be explicit.

5. The method by which medical records and questionnaires will be de-identified or the method and appropriateness of obtaining a waiver from the new HIPPA regulations.

It is the mission of the American Headache Society to improve the lives of patients with headache. The objective of this study is worthy one, and the American Headache Society would be eager, willing, and most appreciative of the opportunity to discuss the refinements in the survey methodology necessary to achieve a satisfactory and meaningful outcome. The AHS would welcome the opportunity to partner with the FDA in realizing our mutual desire to enhance and safeguard the lives of migraine sufferers.

Sincerely,

Robert B. Daroff MD – President, American Headache Society
Stephen D. Silberstein MD – President Elect, American Headache Society
Richard B. Lipton MD – Immediate Past-President, American Headache Society
David W. Dodick MD – Chair, American Headache Society Triptan Cardiovascular Expert Safety Committee
Paul Winner DO – Treasurer, American Headache Society
Fred Sheftell MD – President, American Council Headache Education

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